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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/603,006	06/23/2003	David S. F. Young	2056.023	1649

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Michael A. Slavin  
McHale & Slavin, P.A.  
2855 PGA Boulevard  
Palm Beach Gardens, FL 33410

EXAMINER
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REDDIG, PETER J

ART UNIT	PAPER NUMBER
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1642

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	Application No. 10/603,006	Applicant(s) YOUNG ET AL.	
	Examiner Peter J. Reddig	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 12 January 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-5 and 7-36 is/are pending in the application.
- 4a) Of the above claim(s) 9-36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5, 7 and 8 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                 | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date: _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                        | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date: _____ | 6) <input type="checkbox"/> Other: \_____   |

## **DETAILED ACTION**

### ***Response to Amendment***

1. The amendment filed on January 12, 2007 in response to the Office Action of July 12, 2006 is acknowledged and has been entered. Claims 1, 7 and 8 have been amended and claim 6 has been cancelled.
2. Claims 9-36 have been previously withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.
3. Claims 1-5, 7 and 8 are pending and currently are currently under consideration.

### ***Rejections Maintained Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 8 remains rejected under 35 U.S.C. 112 for the reasons previously set forth on page 5, section 6 of the Office Action of Office Action of July 12, 2006.

Applicant has amended claim 8 to the method of claim 1 wherein said antibody is a chimeric antibody produced from the isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as accession number PTA-5643 and argues that the metes and bounds of the claim now specifically relate to chimeric antibodies produced from the isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as accession number PTA-4890.

Applicant's arguments have been carefully considered, but have not been found persuasive and the rejection is maintained because the term chimeric, as previously set

forth in the Office Action of November 2, 200, is generic to a class of antibodies which are products of genetic shuffling of antibody domains and other active proteins. In the absence of a definition of the term "chimeric" in the specification, it cannot be determined to what the claims are drawn.

Thus the amended claim remains indefinite and the rejection is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-5, 7 and 8 remain rejected for the reasons previously set forth in the Office Action of July 12, 2006, section 9, pages 11-14.

Applicants argue that the specification teaches use of body weight as a surrogate marker of disease progression in a xenograft model of prostate cancer in SCID mice, and further goes on to indicate a reduction of tumor burden in both breast and prostate tumors as a result of treatment with the instant PTA-4890 antibody. Applicants argue that it is improper to limit the claims to a specific exemplary embodiment. The claims are drawn to treatment of a human tumor wherein the tumor expresses an antigen which specifically binds to the isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as accession number PTA-4890. Further, the rejection on the basis of alleged failure to treat metastatic disease is not understood.

Applicants argue that firstly, all cancers do not metastasize. Secondly, the demonstration that tumor burden is reduced or reversed by treatment with the claimed antibody and that weight loss is prevented is indicative of a delay in disease progression, is evidence, in and of itself of a delay in disease progression.

Applicants argue that that a valid model could be easily developed for any cancer expressing such an antigen to codify reduction of body weight as a surrogate marker of disease progression, and for this and the reasons stated above, the rejection should therefore be withdrawn and the claims passed to issue.

Applicant's arguments have been carefully considered, but have not been found persuasive.

In regard to Applicant's argument that it is improper to limit the claims to a specific exemplary embodiment, all questions of enablement are evaluated against the claimed subject matter and the focus of the examination inquiry is whether everything within the scope of the claim is enabled, see MPEP 2164.08 [R-2]. Thus, although exemplification is not required, the claims can be limited to those embodiments that are enabled.

As drawn to the rejection on the basis of metastatic disease, the Office determines the scope of claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction "in light of the specification as it would be interpreted by one of ordinary skill in the art", see MPEP 2111. Given that, as previously set forth in section 9, the art recognizes that cancer progression is defined as the tendency of tumors to become more malignant as they grow and malignancy is the essential property of cancer cells that is demonstrated by their ability to proliferate indefinitely, to invade surrounding tissue, and to metastasize to other organs (p. 399 Tannock, I. F. and Hill, H. P., The Basic Science of Oncology, 1992, previously cited on page 11 of the office action of November 2, 2006) and given that no limiting definition of disease progression is given in the specification, it is proper to assume for examination

purposes that disease progression is the tendency of tumors to become more malignant as they grow, i. e. metastatic. Although the specification teaches that PTA-5643 prevented body weight gain and hypothesizes that this indicates delayed disease progression, given that, as previously cited on page 12 of the office action of November 2, 2006, Hu et al. teaches assessment of body weight **and** abdominal circumference is an imprecise way to assess tumor burden **and** ascites volume, there is no indication in the specification or the art of record that measurement of body weight **alone** indicates disease progression, i. e. the development of metastatic disease. In other words, body weight indicate may only reflect the size of the primary tumor and not the development or inhibition of metastatic tumors at distant sites. Although applicant argues that a valid model could be easily developed to codify body weight as a surrogate marker of disease progression, the development of such a model is not commensurate in scope with the claims and, furthermore, neither the specification nor the art of record teaches what would be required to develop such a model, thus undue experimentation would be required to make and use said model.

Thus, Applicants' arguments have not been found persuasive and the rejection is maintained.

***New Grounds of Rejection***

***Claim Rejections - 35 USC § 112***

6. If Applicants were able to overcome the rejections set forth above under 35 U.S.C. 112, first paragraph, claim 4 would still be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claim 4 is drawn to the method of claim 1, wherein said antibody activates complement.

The specification teaches that there are five classes of antibodies and each is associated with a function that is conferred by its heavy chain. It is generally thought that cancer cell killing by naked antibodies are mediated either through antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). For example murine IgM and IgG2a antibodies can activate human complement by binding the C-1 component of the complement system thereby activating the classical pathway of complement activation which can lead to tumor lysis. For human antibodies, the most effective complement activating antibodies are generally IgM and IgG1. Murine antibodies of the IgG2a and IgG3 isotype are effective at recruiting cytotoxic cells that have Fc receptors which will lead to cell killing by monocytes,

macrophages, granulocytes and certain lymphocytes. Human antibodies of both the IgG1 and IgG3 isotype mediated ADCC, see para. bridging p. 14 and 15.

One cannot extrapolate the teachings of the specification to the enable the claim because no nexus has been established between PTA-4890 and activation of complement and because it is well known in the art that not all antibodies activate complement.

In particular, Dillman (Annals of Internal Medicine, 1989 111:592-603) teaches that different classes and subclasses of mouse immunoglobulins have different abilities to activate complement because of differences in the Fc portion of the heavy chain, see p. 593, left column. Dillman teaches that the best results for complement activation for murine antibodies are obtained with IgM and IgG3, while IgG2A, IgG1 and IgG2B are generally ineffective.

Given the above and given Young et al. (US Pat. No. 7,009,040 B2, 2003) teach that the isotype of PTA-4890 (7BD-33-11A) is IgG2a, see Table 3, and without any empirical evidence that PTA-4890 activates complement, one could not reasonably predict that said antibody will activate complement. Thus undue experimentation would be required to determine if a monoclonal antibody PTA-4890 activates complement.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

7. If Applicants were able to overcome the rejections set forth above under 35 U.S.C. 112, first paragraph, claim 1-5, 7 and 8 would still be rejected under 35 U.S.C. 112, first paragraph,



because the specification, while being enabling for a method of extending survival and delaying disease progression by treating a human **breast or prostate** tumor in a mammal, wherein said tumor expresses an antigen which specifically binds to a monoclonal antibody or antigen binding fragment thereof which has the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as accession number PTA-4890 comprising administering to said mammal said monoclonal antibody in an amount effective to reduce said mammal's tumor burden, whereby disease progression is delayed and survival is extended, *does not* reasonably provide enablement for a method of extending survival and delaying disease progression by treating a **human tumor** in a mammal, wherein said tumor expresses an antigen which specifically binds to a monoclonal antibody or antigen binding fragment thereof which has the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as accession number PTA-4890 comprising administering to said mammal said monoclonal antibody in an amount effective to reduce said mammal's tumor burden, whereby disease progression is delayed and survival is extended. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the

amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method of extending survival and delaying disease progression by treating **a human tumor** in a mammal, wherein said tumor expresses an antigen which specifically binds to a monoclonal antibody or antigen binding fragment thereof which has the identifying characteristics of a monoclonal antibody encoded by a clone deposited with the ATCC as accession number PTA-4890 comprising administering to said mammal said monoclonal antibody in an amount effective to reduce said mammal's tumor burden, whereby disease progression is delayed and survival is extended.

This means that the method can be used for any human tumor.

The specification teaches that in *in vivo* models of breast and prostate cancer PTA-4890 could increase survival and reduce tumor burden, see Examples 1-4.

One cannot extrapolate the teaching of the specification to the scope of the claims because the art teaches that PTA-4890 is selective for breast and prostate cancer cells in its cytotoxic activity and the heterogeneity of cancers and their response to treatment is well known in the art.

1) In particular, as drawn to the heterogeneity of cancers, Young et al. (US Pat. No. 7,009,040 B2, 2003) teach that PTA-4890 (7BD-33-11A) was selectively cytotoxic in breast and prostate cancer cells, see column 10 and Table 2. Furthermore, Young et al. teach that the antibodies were selective in their activity since not all cancer cell types were susceptible, see columns 10 and 11.

Furthermore, the art teaches that cancers comprise a broad group of malignant neoplasms divided into two categories, carcinoma and sarcoma. The carcinomas originate in epithelial tissues while sarcomas develop from connective tissues, see Taber's Cyclopedic Medical Dictionary (1985, F.A. Davis Company, Philadelphia, p. 274). Given that not all cancers originate from the same tissue types, it is expected and known that cancers originate from different tissue types have different structures as well as etiologies and would present differently. Thus, it would not be predictably expected that a nexus, for example drawn to a connection between PTA-4890 and extending survival, would be established between two cancer types that arose from different tissue types. Further, it is well known that even two carcinomas that present on the same organ have significant differences in etiology and genetic constitution. For example, Busken, C et al, (Digestive Disease Week Abstracts and Itinerary Planner, 2003, abstract No:850), teach that there is a difference in COX-2 expression with respect to intensity, homogeneity, localization and prognostic significance between adenocarcinoma of the cardia and distal esophagus, suggesting that these two cancers have different etiology and genetic constitution (last five lines of the abstract). Furthermore Krontiris and Capizzi (Internal Medicine, 4th Edition, Editor-in-chief Jay Stein, Elsevier Science, 1994 Chapters 71-72, pages 699-729) teach that the various types of cancers have different causative agents, involve different cellular mechanisms, and, consequently, differ in treatment protocols. Furthermore, chemotherapeutic agents are frequently useful against a specific type of neoplasm and, especially with the unpredictability of the art, there are no drugs broadly effective against all forms of cancer, see Carter, S. K. et al. Chemotherapy of Cancer; Second edition; John Wiley & Sons: New York, 1981; appendix C. Given the above, it is clear that it is not possible to predictably

extrapolate a correlation between PTA-4890 and extending survival in any tumor type other than breast and prostate cancer, based on the information in the specification and known in the art without undue experimentation.

Applicant is reminded that MPEP 2164.03 teaches “the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

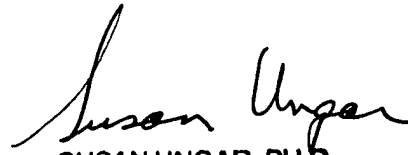
The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

8. All other objections and rejections set forth in the Office action of July 12, 2006 are withdrawn.
9. No claims allowed.
10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J. Reddig/  
Examiner  
Art Unit 1642

  
SUSAN UNGAR, PH.D  
PRIMARY EXAMINER